CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Trifloxystrobin

Chemical Code # 5321, Tolerance # 52415
SB 950 # NA

Original: 5/17/00
Revised: 6/26/01

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, possible adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	No data gap, no adverse effect

Toxicology one-liners are attached.

All record numbers through 171133 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T177171.doc

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

** 062; 160208; "24-Month Carcinogenicity and Chronic Toxicity Study in Rats"; (R. Gerspach, Novartis Crop Protection AG, Toxicology/Experimental Toxicology, 4332 Stein, Switzerland; Test No. 943038; 10/22/97); Seventy rats/sex/group were fed CGA-279202 Technical (purity: 96.4%) in the diet at concentrations of 0, 50, 250, 750 or 1500 ppm ((M): 0, 1.95, 9.81, 29.7, 62.2 mg/kg/day, (F): 0, 2.22, 11.37, 34.5 and 72.8 mg/kg/day, respectively) for up to 2 years. An additional 10 animals/sex/group were included in an interim sacrifice after 53 weeks of treatment. The greater percentage of the males in the 750 (68%) and 1500 (80%) ppm groups and the females in the 1500 (80%) ppm group survived to the termination of the study than did the animals in the control group ((M) 34%, (F) 66%). The males in the 1500 ppm treatment group had a lower mean body weight ($p<0.01$) over the course of the study. Likewise, the females in the 750 and 1500 ppm groups had lower mean body weights ($p<0.01$) than did the control females. Food consumption was reduced significantly for the 1500 ppm females during the first year of treatment. For the hematology, clinical chemistry and urinalysis data, isolated values were statistically significant. However, there were no results indicative of a treatment-related effect. No treatment-related effects were indicated by the ophthalmological observations. Although some of the relative organ weights were significantly increased, the increases were largely due to the decreased body weights observed for the animals in the 1500 ppm group. There were no apparent treatment-related effects indicated for either non-neoplastic nor neoplastic lesions. **No adverse effects indicated. NOEL:** (M/F) 250 ppm ((M) 9.81 mg/kg/day, (F) 11.37 mg/kg/day) (based upon the lower mean body weight for the 750 and 1500 ppm treatment groups). **Study acceptable.** (Moore, 5/5/98)

CHRONIC TOXICITY, RAT

See Combined, Rat.

CHRONIC TOXICITY, DOG

** 055; 160201; "12-Month Chronic Oral Toxicity Study in Beagle Dogs"; (B. Altmann; Toxicology, Novartis Crop Protection AG, 4332 Stein, Switzerland; Test No. 943041; 12/2/97); Four dogs/sex/group were treated orally with 0, 2, 5, 50 or 200 mg/kg/day of CGA-279202 Technical (purity: 96.4%) in gelatin capsules for 12 months. No mortality resulted from the treatment. Animals in the 200 mg/kg/day group suffered from an increased frequency and severity of diarrhea and vomiting. Dark discoloration of the hair and skin of the paws, thorax and abdomen was noted for animals in the 50 and 200 mg/kg/day treatment groups. Food consumption was significantly reduced ($p<0.05$) in the high dose female group for weeks 3 and 4. However, treatment did not affect the mean body weight values. Although some of the hematology parameters for the treated animals were statistically different from those of the control animals, none of the parameters demonstrated a significant treatment effect. In the clinical chemistry, mean serum albumin levels were reduced for the males in the 50 ($p<0.05$) and 200 mg/kg groups ($p<0.01$) for the three sampling times. The albumin level for the females was not affected. Total bilirubin was reduced at weeks 13 and 26 for the 200 mg/kg males ($p<0.05$) and all three sampling times for the 200 mg/kg females (13 and 52 weeks, $p<0.05$, 26 weeks, $p<0.01$). Triglycerides were increased for the 200 mg/kg males at 13 and 52 weeks ($p<0.01$) and for the 200 mg/kg females at 13 ($p<0.05$) and 26 weeks ($p<0.01$). Mean serum alkaline phosphatase activities were increased for the 200 mg/kg males at all sampling times ($p<0.01$) and for the 50 mg/kg males at 26 ($p<0.05$) and 52 weeks ($p<0.01$). The activities for the 200 mg/kg females were increased at week 52 ($p<0.05$). There were no treatment-related effects upon the urinalysis parameters. In the necropsy, the mean liver and testes weights were increased for the 50 ($p<0.05$) and 200 mg/kg males ($p<0.01$). The mean relative liver weight was increased for the 200 mg/kg male group ($p<0.01$). The mean relative testes weights were increased for the 50 ($p<0.05$) and 200 mg/kg groups ($p<0.01$). The mean relative liver weight was increased for the 200 mg/kg females ($p<0.01$). An increased number of animals exhibited hepatocellular hypertrophy in the 50 mg/kg females (3) and the 200 mg/kg males (3) and females (4). Likewise, bone marrow

hypocellularity was noted for a greater number of animals in the 200 mg/kg group (6 vs. 3 for the controls). **No potential adverse effect indicated**. **NOEL:** (M/F) 5 mg/kg/day (based upon increased incidence of clinical signs and the increased mean liver weight or hepatocellular hypertrophy in the 50 mg/kg/day treatment group). **Study acceptable.** (Moore, 4/30/98)

ONCOGENICITY, RAT

See Combined, Rat.

ONCOGENICITY, MOUSE

** 056, 163, 173; 160202, 168382, 171131; "18-Month Carcinogenicity Study in Mice"; (R. Gerspach; Toxicology/Experimental Toxicology, Novartis Crop Protection AG, 4332 Stein, Switzerland; Test No. 943039; 10/22/97); Fifty mice/sex/group were treated in the diet with 0, 30, 300, 1000, or 2000 ppm ((M): 0, 3.90, 39.4, 131.1, and 274 mg/kg/day, (F): 0, 3.51, 35.7, 124.1, and 246 mg/kg/day) for 18 months. An additional ten animals/sex/group were treated for 39 weeks for an interim examination. Also, another ten animals/sex/group were treated for 52 weeks prior to being bled for hematological evaluation. There was no treatment-related effect upon survival. Mean body weights were significantly reduced for the females in the 1000 and 2000 ppm groups ($p<0.01$). The mean liver weights were increased for the 2000 ppm males after both 39 and 79 weeks of treatment ($p<0.01$). Likewise, mean liver weights were increased for the 1000 and 2000 ppm females after 79 weeks of treatment ($p<0.01$). Mean relative liver weights were increased for the 1000 ppm (week 79) and 2000 ppm males and females (weeks 39 and 79) ($p<0.01$). This effect was accompanied histologically by an increased incidence in single cell necrosis and/or necrosis in the livers of the males and females in the 1000 and 2000 ppm groups. In addition, the incidence of hepatocellular hypertrophy was increased for the females in the 1000 and 2000 ppm groups. The number of females suffering from chronic reactive hyperplasia in the mesenteric lymph node was increased in the 1000 and 2000 ppm groups. In conjunction with this effect was an apparent increase in the incidence of malignant lymphoma for the males and females in the 2000 ppm group. Statistical significance was not achieved when the data were evaluated by either the trend test (performed by the registrant) or Fisher's Exact test (performed by the reviewer). **No adverse effect indicated. Chronic Toxicity NOEL:** (M/F) 300 ppm ((M): 39.4mg/kg/day, (F) (35.7 mg/kg/day) (based upon treatment-related effects on the liver of the 1000 ppm group); **No oncogenicity evident.** In record no. 171131, the registrant analyzed the incidence of lymphoma, using the trend test (Peto *et. al.*) to determine p values of 0.10 and 0.24 for the males and females, respectively; the registrant concluded there was no significant statistical difference between the dose groups. Historical control data (record # 168382) indicated that the incidences of malignant lymphoma in mice treated with CGA-279202 for 18 months were not treatment-related and the incidences of malignant lymphoma in the CGA-279202-treated groups are within historical control values. **Study acceptable.** (Moore, 5/19/98, revised, Moore, 11/24/99, updated, Leung, 6/26/01).

REPRODUCTION, RAT

** 061; 160207; "Rat Dietary Two-Generation Reproduction Study"; (S. Khalil, Toxicology/ Experimental Toxicology, Novartis Crop Protection AG, 4332 Stein, Switzerland; Test No. 943045; 10/20/97); Thirty rats/sex/group were dosed in the diet with 50, 750 or 1500 ppm of CGA-279202 Technical (purity: 96.4%) for two generations. The treatment period included 10 weeks prior to mating, 3 weeks of gestation and 3 weeks of lactation. At that time, 30 F1 animals/sex/group were selected as parents and treated for an additional 10 weeks, followed by mating and 3 weeks each for gestation and lactation of the F2 generation. In addition, at the time of the F1 parent selection, the F0 parents were mated a second time (F1b offspring) and maintained through weaning of the offspring. There were no apparent treatment-related parental mortalities. The parents in the 750 and 1500 ppm had lower mean body weights, especially in the F1 groups ($p<0.01$). Food consumption was reduced early in the premating periods for both sexes in the F0 and F1 1500 ppm groups and for the 1500 ppm F0 and F1 females during gestation and lactation ($p<0.01$). There were no treatment-related effects upon the mating, fertility, or litter size. The mean pup weights on day 0 were comparable for all groups. However, by weaning, the mean weights for both the F1 and F2 pups in the 750 and 1500 ppm groups were lower ($p<0.01$). **No adverse effect indicated**. Parental **NOEL:** 50 ppm (based upon lower mean body

weight for the adults in the 750 ppm treatment group); **Reproductive NOEL:** 1500 ppm (72.2 to 301.0 mg/kg/day, no effects on reproductive parameters); **Developmental NOEL:** 50 ppm (2.2 to 10.4 mg/kg/day) (based upon the lower mean body weights of the pups in the 750 ppm treatment group) **Study acceptable.** (Moore, 5/11/98)

TERATOLOGY, RAT

** 059; 160205; "Rat Oral Teratogenicity Study"; (S. Khalil; Short/Long-term Toxicology, Novartis Crop Protection AG, 4002 Basle, Switzerland; Test No. 943042; 3/6/95); Twenty four mated female rats/group were treated orally by gavage with 0, 10, 100 or 1000 mg/kg of CGA-279202 Technical (purity: 96.4%) from day 6 through day 15 of gestation. No deaths resulted from the treatment. Mean food consumption was lower in the 100 mg/kg ($p<0.05$) and 1000 mg/kg groups ($p<0.01$). Mean body weight gain for day 6 to day 11 of gestation was less in the 1000 mg/kg group ($p<0.01$). There were no treatment related effects upon the numbers of resorptions and fetuses and the mean fetal weight. A greater incidence of enlarged thymus ($p<0.05$) was noted for fetuses in the 1000 mg/kg group. **No adverse effect indicated. Maternal NOEL:** 10 mg/kg (based upon reduced food consumption for the dams in the 100 mg/kg group), **Developmental NOEL:** 100 mg/kg (based upon increased number of enlarged thymus in the 1000 mg/kg group); **Study acceptable.** (Moore, 4/30/98)

057; 160203; "Rangefinding Rat Oral Teratogenicity"; (R.E. Fitzgerald; Toxicology Services, Reproduction Toxicology, Novartis Crop Protection AG, 4002 Basle, Switzerland; Test No. 943340; 6/9/93); Seven mated females/group were treated orally by gavage with 0, 10, 100 or 1000 mg/kg of CGA 279202 (purity not given) from day 6 through day 15 of gestation. All of the dams survived the treatment. Food consumption was slightly reduced in the 1000 mg/kg group between day 11 and day 16 of gestation. There were no treatment-related effects upon the fetuses. **Study supplemental.** (Moore, 4/30/98)

TERATOLOGY, RABBIT

** 060; 160206; "Rabbit Oral Teratogenicity"; (S. Khalil; Short/Long-term Toxicology, Novartis Crop Protection AG, 4332 Stein, Switzerland; Test No. 943043; 12/21/94); Nineteen artificially inseminated rabbits/group were treated orally by gavage with 0, 10, 50, 250, or 500 mg/kg of CGA-279202 Technical (purity: 96.4%) from day 7 through day 19 of gestation. One female died in the 50 mg/kg group on day 27. The mean body weight gain was less during days 7 to 12 for the 250 and 500 mg/kg females ($p<0.01$) and during days 12 to 16 for the 500 mg/kg group ($p<0.01$). Mean food consumption was less throughout the treatment period for the 250 and 500 mg/kg groups ($p<0.01$). There were no treatment-related effects upon the fetuses. **Developmental NOEL:** 500 mg/kg; **No adverse effect indicated. Maternal NOEL:** 50 mg/kg (based upon reduced body weight gain and food consumption for the 250 mg/kg group); **Study acceptable.** (Moore, 5/1/98)

058; 160204; "Rangefinding Rabbit Oral Teratogenicity"; (S. Khalil; Short/Long-term Toxicology, Novartis Crop Protection AG, 4332 Stein, Switzerland; Test No. 933142; 3/18/94); Five artificially inseminated rabbits/group were treated by gavage with 0, 20, 100, 500 or 1000 mg/kg of CGA 279202 (purity: 97.1%) from day 7 through day 19 of gestation. No deaths resulted from the treatment. All of the females in the 1000 mg/kg group suffered total resorption of their embryos. The mean body weights and food consumption were significantly reduced for the 500 mg/kg group. In the 100 mg/kg group, mean food consumption was lower between days 7 and 12 of gestation. Mean fetal weight was significantly reduced in the 500 mg/kg group. No fetal abnormalities were evident. **Study supplemental.** (Moore, 5/1/98)

GENE MUTATION

** 063; 160209; "*Salmonella* and *Escherichia*/Mammalian-Microsome Mutagenicity Test"; (Th.

Hertner; Genetic Toxicology, Novartis Crop Protection AG, Basle, Switzerland; Test No. 943074; 9/26/94); *S. typhimurium* strains TA 98, TA 100, TA 102, TA 1535, TA 1357, *E. coli* strain WP2 uvrA were treated for 48 hours at 37° C with CGA-279202 Technical (purity: 96.4%) at concentrations ranging from 312.5 to 5000 µg/plate with and w/o activation in the first experiment and from 61.73 to 5000 µg/plate with and w/o activation in the second experiment. Each treatment level was plated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to activate the test material. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated. Study acceptable.** (Moore, 5/11/98)

**** 064; 160210**; "Gene Mutation Test with Chinese Hamster Cells V79"; (Th. Hertner; Genetic Toxicology, Novartis Crop Protection AG, Basle, Switzerland; Test No. 943075; 7/5/95; Chinese hamster V79 cells were treated with CGA-279202 Technical (purity: 94.6%) at concentrations ranging from 0 to 833.50 µg/ml for 5 hours (activation) or 21 hours (non-activation) at 37° C. Three trials were performed with duplicate samples for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to activate the test material. A treatment-related increase in the mutation frequency was evident for both the non-activated and activated samples. Although the treatment levels were varied for each of the trials, a significant increase in the mutation frequency was noted for treatment levels of 92.6 ($p<0.05$) and 100.0 µg/ml ($p<0.01$) in the first two non-activated trials. For the activated samples, treatment levels of 277.83 and 250.0 µg/ml resulted in a significant increase in mutation frequency ($p<0.01$). Cell survival ranged from 49.7 to 68.3% of the control for these treatment levels. **Potential adverse effect indicated:** increased mutation frequency. **Study acceptable.** (Moore, 5/20/98)

** 066; 160212; "*Salmonella* and *Escherichia*/Mammalian-Microsome Mutagenicity Test"; (E. Deparade; Toxicology, Genetic Toxicology, Novartis Crop Protection AG, CH-4002; Basle, Switzerland; Test No. 973007; 9/18/97); *S. typhimurium* strains TA 98, TA 100, TA 102, TA 1535, TA 1357, *E. coli* strain WP2 uvrA were treated for 48 hours at 37° C with CGA-357261 Technical (Z,E-isomer of CGA-279202) (purity: 99%) at concentrations ranging from 312.5 to 5000 µg/plate with and w/o activation. Two trials were performed. Each treatment level was plated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to activate the test material. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated. Study acceptable.** (Moore, 5/21/98)

** 067; 160213; "*Salmonella* and *Escherichia*/Mammalian-Microsome Mutagenicity Test"; (E. Deparade; Toxicology, Genetic Toxicology, Novartis Crop Protection AG, CH-4002; Basle, Switzerland; Test No. 973025; 9/16/97); *S. typhimurium* strains TA 98, TA 100, TA 102, TA 1535, TA 1357, *E. coli* strain WP2 uvrA were treated for 48 hours at 37° C with CGA-373466 Technical (Metabolite of CGA-279202) (purity: 99 $\pm$ 2%) at concentrations ranging from 312.5 to 5000 µg/plate with and w/o activation. Two trials were performed. Each treatment level was plated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to activate the test material. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated. Study acceptable.** (Moore, 5/22/98)

** 068; 160214; "*Salmonella* and *Escherichia*/Mammalian-Microsome Mutagenicity Test"; (E. Deparade; Toxicology, Genetic Toxicology, Novartis Crop Protection AG, CH-4002; Basle, Switzerland; Test No. 973065; 10/29/97); *S. typhimurium* strains TA 98, TA 100, TA 102, TA 1535, TA 1357, *E. coli* strain WP2 uvrA were treated for 48 hours at 37° C with NOA-414412 Technical (metabolite of CGA-279202) (purity: 95 $\pm$ 2%) at concentrations ranging from 312.5 to 5000 µg/plate with and w/o activation. Two trials were performed. Each treatment level was plated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to activate the test material. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated. Study acceptable.** (Moore, 5/22/98)

CHROMOSOME EFFECTS

** 065; 160211; "Micronucleus Test, Mouse"; (Th. Hertner; Genetic Toxicology, Novartis Crop Protection AG, Basle, Switzerland; Test No. 943078; 2/1/95); Five animals/sex/group/time point were

treated orally by gavage with a dose of 0 (vehicle control), or 5000 mg/kg of CGA-279202 Technical (purity: 96.4%) and euthanized 16, 24 or 48 hours after dosing. An additional 5 animals/sex were treated with the positive control (cyclophosphamide, 64 mg/kg) or 1250 or 2500 mg/kg of the test material and euthanized 24 hours after dosing. Bone marrow samples from the femur were examined and the ratio of polychromatic (PCE) to normochromatic erythrocytes (NCE) and the percentage of PCE with a micronucleus were determined. No treatment-related increase in the number of polychromatic erythrocytes with a micronucleus was noted. **No adverse effect indicated. Study acceptable.** (Moore, 5/21/98)

** 069; 160215; "Cytogenetic Test on Chinese Hamster Cells *in Vitro*"; (Th. Hertner; Genetic Toxicology, Novartis Crop Protection, AG, Basle, Switzerland; Test No. 943076; 12/6/94); Chinese hamster ovary (CCL 61 (CHO K1)) cells were exposed to CGA-279202 Technical (purity: 96.4%) at concentrations ranging from 0 to 200 µg/ml with and w/o activation (trial #1) or 0 to 6.25 µg/ml w/o activation (trials #2 and 3) or 0 to 100 µg/ml with activation (trials #2 and 3). In trials 1 and 2, the cells were exposed to the test material for 18 hours w/o activation or 3 hours with activation, followed by a 15 hour recovery period. In trial #3, cells were treated for 42 hours w/o activation or 3 hours with activation, followed by a 39 hour recovery period. Incubations were performed at 37° C with duplicate cultures/treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to activate the test material. No treatment-related increase in the incidence of chromatid or chromosomal aberrations was noted except for the 50 µg/ml treatment level of the 42 hour activation/recovery group ($p<0.01$). However, the value was within the historical control range. For the non-activated samples, the concentration of the test material at which cytotoxicity was evident was quite different between trials #1 and 2. In the first trial, concentrations ranging from 0.781 to 3.125 µg/ml were used to determine the incidence of chromosomal aberrations as compared to 0.049 to 0.195 µg/ml for trial #2. However, in trial #2, 0.781 to 3.125 µg/ml were demonstrably cytotoxic. The flow cytometry measurements in trial #1 indicated that the DNA distribution profile was altered from that of the control for the three concentrations used to determine the incidence of chromosomal aberrations. **No adverse effect indicated. Study acceptable.** (Moore, 5/26/98)

DNA DAMAGE

** 070; 160216; "Autoradiographic DNA Repair Test on Rat Hepatocytes *in Vitro*"; (Th. Hertner; Genetic Toxicology, Novartis Crop Protection, AG, Basle, Switzerland; Test No. 943077; 6/9/95); Primary rat hepatocyte cultures were exposed to CGA-279202 Technical (purity: 96.4%) at concentrations ranging from 0.39 to 50 µg/ml for 16 to 18 hours at 37° C. Vehicle control (DMSO: 1%) and positive control (2-AAF: 10 µg/ml) cultures were included in the assay. There were 3 cultures per treatment level in two trials. There was no treatment-related increase in unscheduled DNA synthesis. **No adverse effect indicated. Study acceptable.** (Moore, 5/27/98)

NEUROTOXICITY

52415-048, -143, -175; 160194, 163865, 171133; "Acute Oral Neurotoxicity Study in Rats" (Classen, W., Toxicology/Experimental Toxicology, Novartis Crop Protection AG, Stein, Switzerland, Test #s 973005 and 950026, 12/2/97 and 8/10/98). 818. CGA 279202 tech. (Batch code P. 405009 , 96.4% purity), suspended in 0.5% (w/v) carboxymethylcellulose in 0.1% (w/v) aqueous polysorbate 80, was administered by gavage in a single dose at concentrations of 0 (vehicle) and 2000 mg/kg to 10 Tif:RAIf, hybrids of RII/1xRII/2 (Sprague-Dawley) rats per sex per dose level. One male animal at 2000 mg/kg on day 2 was found recumbent and was sacrificed in moribund condition; the condition of this animal is not considered treatment-related. No treatment-related clinical signs were observed in the surviving animals. FOB and motor activity assessments revealed no treatment-related differences between the control and treated dose groups. Macroscopic and microscopic examination revealed no treatment-related findings. **No adverse effects indicated.** NOEL (M/F)> 2000 mg/kg (based on the absence of clinical signs). Originally **unacceptable but possibly upgradeable** with submission of positive control data (Corlett and Leung, 4/21/98). Subsequently, positive control data on triadimefon submitted were not sufficient to eliminate deficiency of this study because additional positive control groups exhibiting central and peripheral nervous system pathology were not included. Resubmission under record no. 171133 does

not address this deficiency. Status unchanged. (Updated, Leung and Corlett, 1/5/99, Moore, 11/24/99).

52415-174; 171132; "Acute Oral Rangefinding Neurotoxicity Study in Rats"; (W. Classen; Novartis Crop Protection AG, Toxicology/Experimental Toxicology, 4332 Stein, Switzerland; Test No. 973004; 9/10/97); Three rats/sex/group were treated orally by gavage with 0, 1000, 2000, or 3500 mg/kg of CGA-270202 Technical (purity: 96.4%) with a single dose and observed for 4 days. Increased incidence of piloerection and/or reduced activity were evident in both sexes on the first day of dosing at 3500 mg/kg. There was no effect upon body weight gain or food consumption. Other than the reduced activity and piloerection, no other neurologically-related effects were noted in the abbreviated Functional Observational Battery which was employed. **Supplemental study**. (Moore, 11/24/99)

SUBCHRONIC STUDIES

051; 160197; "28-days Range Finding Toxicity Study in Rats (Administration in Food)" (Gerspach, R., Ciba-Geigy Limited, Short/Long-term Toxicology, Stein, Switzerland, Test No. 933099, 11/14/94). CGA 279202 tech. (Batch No. KGL-4617/5, purity=96.2%), was admixed to the pelleted food at concentrations of 0 (pelleted food without test article), 200, 1000, 4000 or 12000 ppm (0, 16.5, 84.4, 337, or 1074 mg/kg/day, respectively, for males and 0, 16.4, 84.1, 327, or 1005 mg/kg/day, respectively, for females) and fed to 5 Tif:RAIf (SPF), hybrids of RII/1xRII/2 (Sprague-Dawley derived) rats per sex per dose level continuously for a period of 4 weeks. No animals died. Soft feces, in all males and females at 4000 ppm and in one male and all females at 12000 ppm, and diarrhea, in one male at 4000 ppm and in all males and one female at 12000 ppm were observed. A statistically significant decrease in mean body weights was observed in males at 4000 and 12000 ppm and in females at 12000 ppm was observed. A statistically significant and dose-related increase in mean relative liver weights in males at 4000 and 12000 ppm was observed. Macroscopic examination revealed no treatment-related changes. **No adverse effects.** NOEL (M)=84.4 (1000 ppm) and (F) 84.1 mg/kg/day (1000 ppm) (based on clinical signs). **Supplemental study** (animals were treated for only 28 days, only 5 animals per sex per dose level were used, no ophthalmological examinations on the eyes of the test animals were conducted, and no histopathology was performed). (Corlett, 4/27/98)

052; 160198; "3-Month Oral Toxicity in Rats (Administration in Food)" (Gerspach, R., Ciba-Geigy Limited, Short/Long-term Toxicology, Stein, Switzerland, Study Number 933164, 1/19/95). 821. CGA 279202 tech. (Batch No. KGL-4617/5, purity=96.2%) was admixed to the pelleted food at concentrations of 0, 100, 500, 2000, or 8000 (females only) ppm (0, 6.44, 30.6, or 127 mg/kg/day, respectively, for males and 0, 6.76, 32.8, 133, or 618 mg/kg/day, respectively, for females) and fed to 15 Tif: RAIf (SPF) hybrids of RII/1 x RII/2 (Sprague-Dawley derived) rats per sex per dose level [with 10 additional rats per sex per dose level at the control and high dose levels to test recovery (4 week recovery period used)] continuously for a period of 3 months. Treatment-related deaths included of 1 male and 1 female at 2000 ppm and 5 females at 8000 ppm. Soft feces and piloerection were observed in all females at 8000 ppm. A statistically significant decrease in mean body weights was observed in males at 2000 ppm and in females at 8000 ppm at Weeks 4, 8, and 13 but not at Week 17. A dose-related increase in mean relative liver weights was observed in both males at 500 and 2000 ppm and in females at 2000 and 8000 ppm at Week 14 but not Week 18. Microscopic examination revealed hepatocyte hypertrophy in males at 2000 ppm and in females at 8000 ppm at Week 14 but not at Week 18. NOEL (M)=30.6 mg/kg/day and (F)=32.8 mg/kg/day (500 ppm; based on a dose-related increase in pancreas atrophy. **Acceptable.** (Corlett, 5/8/98)

050; 160196; "28-Day Range Finding Toxicity Study in Beagle Dogs" (Altmann, B., Ciba-Geigy Limited, Short/Long-term Toxicology, Stein, Switzerland, Test No. 933163, 9/28/94). CGA 279202 tech. (Batch No. KGL4617/, purity=96.2%) was administered orally (capsule) to 2 Beagle dogs per sex per dose level at dose levels of 0 (empty capsule), 20, 50, or 150 mg/kg once daily for a period of 28 days after which the high dose group animals were dosed further at 500 mg/kg daily for 21 days. No animals died. Treatment-related clinical signs included moderate diarrhea and vomiting in both males and females at 150/500 mg/kg/day. Statistically significant increases
in mean relative liver (males and females), kidney (males), and spleen weights (females) at 150/500 mg/kg/day were observed. Microscopic examination revealed congestion of the splenic red pulp in one

male and two females at 150/500 mg/kg/day. **No adverse effects.** NOEL (M/F)=50 mg/kg/day (based on clinical signs and increased mean relative liver weights). **Supplemental study** (animals were treated for only 28-49 days and only 2 animals per sex per dose level were used). (Corlett, 5/12/98)

053; 160199; "3-Month Subchronic Oral Toxicity Study in Beagle Dogs" (Altmann, B., Ciba-Geigy Limited, Short-/Long-term Toxicology, Stein, Switzerland, Test No. 943040, 6/26/96). 821. CGA 279202 tech. (Batch No. P. 405009, purity=96.4%) was administered orally (capsule) to 4 Beagle dogs per sex per dose level at dose levels of 0 (empty capsule), 5, 30, 150, or 500 mg/kg once daily for a period of 91 to 94 days. One male at 500 mg/kg/day was sacrificed in moribund condition. Treatment-related moderate to severe diarrhea and vomiting in both males and females at 150 and 500 mg/kg/day were observed. Statistically significant decreases in mean body weight and mean food consumption in males and females at 500 mg/kg/day were observed. Treatment-related decreases in several blood chemistry parameters in both males and females at 500 mg/kg/day including mean creatinine, bilirubin, protein, albumin, alanine amino-transferase, and creatine kinase levels were observed. Treatment-related increases in mean relative liver weights in males at 150 and 500 mg/kg/day and in females at 500 mg/kg/day, and in mean relative kidney weights in males and females at 500 mg/kg/day were observed. Treatment-related emaciation of the whole body was observed in males and females at 500 mg/kg/day. Microscopic examination revealed treatment-related hypertrophy of hepatocytes in males at 150 and 500 mg/kg/day and in females at 500 mg/day/day and treatment-related hyperplasia of the gall bladder epithelium in males and females at 500 mg/kg/day. **No adverse effects.** NOEL (M/F)=30 mg/kg/day (based on clinical signs). **Acceptable**. (Corlett, 5/20/98)

049; 160195; "3-Month Range Finding Toxicity Study in Mice (Administration in Food)" (Gerspach, R., Ciba-Geigy Limited, Short/Long-term Toxicology, Stein, Switzerland, Test No. 933165, 11/14/94). CGA 279202 tech. (Batch No. KGL4617/5, purity=96.2%), was admixed to the pelleted food at concentrations of 0 (pelleted food without test article), 500, 2000, or 7000 ppm (0, 76.9, 315, or 1275 mg/kg/day, respectively, for males and 0, 110, 425, or 1649 mg/kg/day, respectively, for females) and fed to 10 Tif:MAGf (SPF), hybrids of NIH x MAG albino mice per sex per dose level continuously for a period of 3 months. One female at 500 ppm died on day 92. No treatment-related clinical signs were observed. A statistically significant and dose-related increase in mean relative liver weights in males and females at 2000 and 7000 ppm and a statistically significant increase in mean relative spleen weight in females at 7000 ppm were observed. In female test animals at 7000 ppm, macroscopic examination revealed enlarged liver in 2 animals and enlarged spleen in 6 animals. Microscopic examination revealed dose-related increases in hypertrophy of hepatocytes and in splenic hemosiderosis in both males and females at 7000 ppm. **No adverse effects.** NOEL (M)=76.9 mg/kg/day (500 ppm) and (F)=110 mg/kg/day (500 ppm) based on an increase in mean relative liver weights. **Supplemental study** (no clinical biochemistry determinations on the blood of the test animals and no ophthalmological examinations on the eyes of the test animals were conducted). (Corlett, 4/23/98)

054; 160200; "28-Day Repeated Dose Dermal Toxicity Study in the Rat" (Gerspach, R., Ciba-Geigy Limited, Short/Long-term Toxicology, Stein, Switzerland, Study Number 943046, 3/5/96). 822. CGA 279202 tech. (Batch No. P. 405009, purity=96.4%), mixed with deionized water in 0.5% (w/w) carboxymethylcellulose and 0.1% (w/v) aqueous polysorbate 80, was applied to the clipped skin of 5 Tif: RAIf (SPF) hybrids of RII/1 x RII/2 (Sprague-Dawley derived) rats per sex per dose at concentrations of 0, 10, 100, or 1000 mg/kg/day for 6 hours per day 5 days per week for 4 weeks using an occlusive dressing. All animals survived. No treatment-related clinical signs or signs of local irritation were observed. Hematology and clinical biochemistry performed on the test animals revealed no treatment-related effects. Dose-related and statistically significant increases in mean relative liver and kidney weights were observed in males at 1000 mg/kg/day. Macroscopic and microscopic examination revealed no treatment-related findings. **No adverse effects.** NOEL (systemic, M)= 100 mg/kg/day (based on mean relative liver and kidney weights), NOEL (systemic, F)=1000 mg/kg/day (based on the absence of treatment-related systemic effects), NOEL (dermal, M/F)=1000 mg/kg/day (based on the absence of treatment-related signs of local irritation). **Acceptable.** (Corlett, 5/27/98)

METABOLISM STUDIES

** 106; 160253; "The Absorption, Distribution and Excretion of [Glyoxyl-Phenyl-(U)-^{14}C] and [Trifluormethyl-Phenyl-(U)-^{14}C] CGA-279202 in the Rat"; (T. Muller; Animal Metabolism, Product Safety Division, Novartis Crop Protection AG, Basle, Switzerland; Report No. PR 13/96; 8/29/96); Male and female rats were dosed by gavage with either [Glyoxyl-Phenyl-(U)-^{14}C] (spec. act. range: 54.3 to 63.5 µCi/mg, radiochemical purity range: >97 to >99%) or [Trifluormethyl-Phenyl-(U)-^{14}C] CGA-279202 (spec. act.: 59.2 µCi/mg, radiochemical purity: >99%). For all of the groups except D2, the animals were dosed with [Glyoxyl-Phenyl-(U)-^{14}C] CGA 279202. In Groups B1 and D1, urine and feces samples were collected up to 7 days from 5 animals/sex dosed with 0.5 or 100 mg/kg of the test material, respectively. For Group C1, 5 animals/sex were pretreated for 14 days with 0.5 mg/kg of unlabelled CGA 279202 (purity: 99.7%), followed by 0.5 mg/kg of the labelled test material. Urine and feces samples were likewise collected from these animals for up to 7 days. In Group D2, 5 animals/sex were dosed with 100 mg/kg of [Trifluormethyl-Phenyl-(U)-^{14}C] CGA-279202 and urine and feces samples were collected up to 7 days. Twelve animals/sex were dosed with either 0.5 or 100 mg/kg of the test material in Groups F1 and 5 and Groups F2 and 6, respectively. Tissue residues were determined at 4 time points based upon pharmacokinetic determinations derived from the previous groups. The bile ducts of animals in Group G were cannulated. In Groups G1 and 3, 6 males and 5 females were treated with 0.5 mg/kg of the test material. Six males and 4 females were dosed with 100 mg/kg of the test material in Groups G2 and 4, respectively. At the low dose level, 56 to 65% of the dose was absorbed with 41 to 47% of the dose recovered from the bile. In the high dose group, 25 to 45% of the dose was absorbed with 19 to 35% of the dose recovered from the bile. In the low dose treatment, 18 to 19% and 79% of the dose was excreted in the urine and feces, respectively, of the males. For the females, 35 to 42% was excreted in the urine and 56 to 63% in the feces. Pretreatment with unlabelled test material did not alter the pattern of excretion. In the high dose groups, the males excreted 10 to 12% and 82 to 84% in the urine and feces, respectively. The females excreted 27% in the urine and 64 to 66% in the feces. Very minimal levels of radiolabel were recovered from the expired air of the animals in Group D2. The half lives for the depletion of radiolabel from the tissues ranged from 13 to 42 hours except for the spleen and blood of the high dose females (68 and 82 hours, respectively). The times to maximal concentration of the test material in the blood were either 12 to 24 hours after dosing. The times to 2 maximal concentration ranged from 23 to 67 hours after dosing. Residual retention of the radiolabel in the carcass after 7 days was very minimal with 0.3 to 0.5% of the dose administered recovered. **Study acceptable.** (Moore, 6/2/98)

073; 160219; "The Metabolism of [Glyoxyl-Phenyl-(U)-^{14}C] and [Trifluormethyl-Phenyl-(U)-^{14}C] CGA-279202 in the Rat"; (P. Thanei; Animal Metabolism, Novartis Crop Protection AG, Basle, Switzerland; Project Report 12/97; 11/14/97); Excreta recovered from the previous toxicokinetic study (see Vol. #52415-106, rec. #160253) were analyzed for specific metabolites and the metabolic pathway determined. In addition, samples from two additional dosed groups of male and female rats were included in the analyses. In Group B2, animals were treated with 0.5 mg/kg of [Trifluormethyl-Phenyl-(U)-^{14}C] CGA-279202 and urine (0-48 hrs) and fecal (0-72 hrs) samples collected. A second G4a group of bile-cannulated females was included in the study in order to augment the data collected from the original group. Thirty five metabolites were isolated and identified from the urine, feces and bile samples. Major metabolic pathways included 1) hydrolysis of the methyl ester to the corresponding acid, 2) O-demethylation of the methoxyimino group, and 3) oxidation of the methyl side chain to a primary alcohol, followed by further oxidation to the carboxylic acid. This last reaction was a more prominent metabolic pathway in the female rats with the resultant isolation of major sex-specific urinary metabolites. Cleavage of the glyoxyl-phenyl and trifluoromethyl-phenyl moieties accounted for 10% of the dose. For the trifluoromethyl phenyl fragment, oxidation of the hydroxyimino group led to the formation of a nitro compound and oxidation of the methyl group resulted in the formation of the carboxylic acid. In addition, hydrolysis of the imino group formed an intermediate ketone with succeeding reactions ultimately leading to trifluoromethyl benzoic acid. For the glyoxyl-phenyl moiety, oxidation resulted in the formation of a benzoic acid. O-demethylation of the methoxyimino group resulted in the hydroxyimino compound. Hydrolysis of the imino group yielded the a-keto acid followed by decarboxylation to the phthalic acid. Conjugates with glucuronide or sulfate were isolated from the bile. Four to 7% and 31 to 47% of the low and high doses, respectively, were eliminated in feces as the unmetabolized test material. The absorbed dose was predominantly isolated in the bile. Further processing returned the test material and/or metabolites to the intestinal tract and elimination in the feces or reuptake via the enterohepatic pathway.

Supplemental Study. (Moore, 6/3/98)

52415-142; 163864; "The Metabolism of [Glyoxyl-Phenyl-(U)-^{14}C] and [Trifluormethyl-Phenyl-(U)-^{14}C] CGA-279202 in the Rat (Admendment 1)" (P. Thanei, Novartis Crop Protection AG, Basle, Switzerland, PR 12/97, Novartis # 712-97, 5/29/98). Additional experimental work has resulted in the identification of NOA 413161 as a metabolite of CGA-279202 in the urine. NOA 413161 did not correspond to a distinct metabolite fraction in the High Pressure Liquid Chromatography (HPLC) analytical reference system but to unresolved radioactivity in the range between metabolite fractions U11 and U12. NOA 413161 accounted for less than 0.1% of the administered dose. **Supplemental**. (Leung, 1/4/99).